IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Jan C. SIMON *et al.*

Serial No.: 09/856,694

Filed: August 13, 2001

Art Unit: 1651

Atty Docket No.: 24741-1525

For: HYPERFORIN AS CYTOSTATIC AGENT AND HYPERFORIN OINTMENT OR CREAMS AS APPLICATION FORM

BRIEF ON APPEAL

Appeal from the Primary Examiner

Heller Ehrman
Suite 300
1666 K Street, N.W.
Washington, DC 20006

BRIEF ON APPEAL

Appellants appeal the August 6, 2004 final rejection (the "Final Rejection") of the captioned application to the Board of Patent Appeals and Interferences. Appellants filed a Notice of Appeal on October 20, 2004.

I. REAL PARTY IN INTEREST

UNIVERSITAETSKLINIKUM FREIBURG, as assignee, owns the entire right, title and interest in the captioned application and, therefore, is the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

Appellants are aware of no other current appeals or interferences pertaining to the instant invention. Appellants previously filed a Brief on Appeal for this application but the Patent and Trademark Office reopened the application for prosecution so as to address a defect with one of its references.

III. STATUS OF CLAIMS

Claims 36-45 and 56 are on appeal. These claims stand finally rejected, as indicated in the final rejection. A copy of the claims on appeal is attached.

Claims 1-19 were cancelled in a Preliminary Amendment on May 24, 2001. Claims 20-35 were cancelled in an Amendment and Response under 37 CFR §1.111 on February 21, 2002. Claim 55 was cancelled in an Amendment under 37 CFR §1.116 on August 2, 2002. Claims 46-55 were canceled and claims 36, 38 and 56 were amended in an Amendment under 37 CFR §1.111 on May 26, 2004.

IV. STATUS OF AMENDMENTS

An amendments was filed October 20, 2004 after the final rejection mailed August 6, 2004. This amendment was not entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention relates to a method for treating a condition, comprising administering to a subject in need thereof an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, wherein said condition is an inflammatory skin condition, a precancerous condition, a geriatric skin condition, or a microbial skin infection. (Specification at 7, line 15; at 9, line 31 to 10, line 12)

In one embodiment, the condition is eczema; in another, the condition is exsiccation eczemas, hyperkeratotic hand and foot eczemas, contact eczemas, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphomas, leukemia, an epithelial pre-cancerous condition, tumor metastases, or an epithelial tumor. (Specification at 10, lines 5-11)

The subject of the treatment may be a mammal. (Specification at 10, lines 18-21)

The method of the invention may use a composition in the form of a topical ointment and the effective amount is at least 15 μg hyperforin per ml of the composition. (Specification at 7, lines 4-8) In another embodiment, the effective amount of such composition is 0.02-20 mg hyperforin per ml of the composition (Specification at 7, lines 4-11); in another, the effective amount is 1-20 mg hyperforin per ml of the composition

(Specification at 7, line 13); in another, the effective amount is either at least 10 mg (Specification at 7, line 13) or at least 15 μg hypericin per ml of the composition (Specification at 7, line 20). In the method of the invention, the hyperforin may be at least 90% pure. (Specification at 12, lines 17-18)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues in this appeal are:

- Whether claims 36-45 and 56 would have been obvious over The Hypericum Homepage (*Hypericum & Depression,* Bloomfield *et al.*, Copyright 1996, Prelude Press, Editor J. Sedillos) in view of *The Merck Manual* (1995-2002) within the meaning of 35 U.S.C. § 103(a).

- Whether claims 36, 38-45 and 56 would have been obvious over Valavichyus "Antitumor Activity of Medicinal Plants from the Lithuanian SSR, USSR 6, Common St. John's Wort Chamomilla Recutita" *Abstract from BIOSIS*, 1986) within the meaning of 35 U.S.C. § 103(a).

- Whether claims 36, 38-45 and 56 would have been obvious over Valavichyus in view of HHP and/or DeCosterd, *Helvetica Chimica Acta*, 72: 464-471 (1989) within the meaning of 35 U.S.C. § 103(a).

The rejected claims do not stand or fall together. Claim 36 is independent and recites a method of treating a condition selected from a group of conditions consisting of inflammatory skin conditions, a precancerous condition, a geriatric skin condition and a microbial skin infection. Claim 38 depends from claim 36 and recites, among other things, leukemia and lymphoma. Although Appellants attempted to make claim 38 independent, and also have a separate claim directed to leukemia and lymphoma, the Examiner did not enter the amendment. Appellants believe that at least two embodiments in claim 38, *i.e.*

leukemia and lymphoma, are separately patentable. Although Appellants acknowledge that they could have filed a Request for Continued Examination instead of filing this Brief on Appeal, Appellants believed that this case is otherwise ready for appeal and would welcome a remand to correct the claim dependency issue.

Appellants also believe that the invention of claim 56 is separately patentable; none of the art of record suggests the purity level recited in this claim.

VII. ARGUMENT

A. Claims 36-45 and 56 would not have been rendered obvious by The Hypericum Homepage in view of The Merck Manual within the meaning of 35 U.S.C. § 103(a).

1. The Rejected Claims

Independent claim 36 recites a method for treating a condition, comprising administering to a subject in need thereof an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, wherein said condition is selected from the group consisting of an inflammatory skin condition, a precancerous condition, a geriatric skin condition, and a microbial skin infection.

Dependent claims 37-38 specify administration of the compound for treating specific conditions. Dependent claim 39 specifies the subject as a mammal. Dependent claims 40-45 prescribe that the composition be a topical ointment and that the effective amount be at least 15 micrograms of hyperforin/ml, 0.02-20 mg/ml or 1-20 mg/ml; or 15 micrograms/ml or 20-150 micrograms/ml hypericin. Claim 56 specifies that the hyperforin be at least 90% pure.

2. The PTO's Case

The U.S. Patent and Trademark Office (the "PTO") asserts that the Hypericum Home Page ("HHP") teaches that extracts of St. John's Wort, which contains hyperforin and hypericin, exhibits anti-inflammatory and antibacterial effects when applied externally or topically and specifically teaches that hyperforin is attributed with anti-inflammatory and antibacterial effects (Final Rejection at 3). The PTO argues that although HHP does not teach a method for treating an inflammatory condition with the claimed effective amounts or for the specific conditions, it would have been obvious to one of ordinary skill in the art to use hyperforin and/or hyperforin and hypericin to treat inflammatory conditions because of the disclosed anti-inflammatory effects (Final Rejection at 3-4).

The PTO further argues that it would have been obvious to one of ordinary skill in the art to optimize effective volumes and concentrations as a matter of routine experimentation (Final Rejection at 4) and that it would have been obvious to one of skill in the art to include a pharmaceutical carrier.

Finally, the PTO asserts that one of ordinary skill in the art would have been motivated to use hyperforin in a method for treating inflammatory conditions with a reasonable expectation of success because of hyperforin's known benefits, as disclosed by HHP (Final Rejection at 4). The PTO cites the *Merck Manual* ("Merck") and Shroot *et al.* (U.S. Patent No. 5,151,534) and Lacefield *et al.* (U.S. Patent No. 4,021,553) as evidence that one of ordinary skill in the art would have known that eczemas are inflammatory diseases (Final Rejection at 4). According to the PTO, one of ordinary skill in the art would have been motivated to combine HHP and Merck, and utilize hyperforin in a method for treating inflammation and eczemas with a reasonable expectation of success.

3. Appellants' Response

The PTO has not presented a *prima facie* case of obviousness. Under the relevant law, the standard for assessing obviousness is (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F. 2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) The PTO has not met this burden.

St. John's Wort extract is not the same thing as hyperforin or hyperforin with hypericin. HHP discusses St. John's Wort extract. Specifically, it states that St. John's Wort contains at least ten different components. It describes some of the therapeutic uses of St. John's Wort, including the use for treating depression. It notes that it has been reported that externally applied St. John's Wort has anti-inflammatory and antibacterial effects and that such effect has been attributed to the hyperforin in the St. John's Wort extract.

It is clear from the HHP disclosure that St. John's Wort extract is a complicated combination of many different ingredients. This is supported by another reference cited by the PTO in connection with the rejection discussed below, Chavez, which states that "[t]he chemical constituents of St. John's Wort are complex, numerous and diverse" and that "[t]he amount of the constituents is related to the harvesting period, the drying process and the storage." (Chavez at 1622) Although HHP mentions hyperforin as possibly being responsible for St. John's Wort having an anti-inflammatory property when used externally, it does not teach the use of a purified, effective amount of hyperforin in a pharmaceutical composition for use in treating an inflammatory skin condition, a precancerous condition, a geriatric skin condition or a microbial skin infection. The PTO admits these deficiencies in HHP. It relies upon what would be "obvious to the skilled artisan" to optimize the effective amount and put it into a carrier" to complete its case.

Appellants also note that the PTO acknowledges that the art considers St. John's Wort oil to be hypercin-free. (Final Rejection at 8, first paragraph). Thus, the PTO must acknowledge that the embodiment whereby hyperforin and hypercin are present, is not addressed by the art of record.

Appellants also point out that it is not clear from HHP what type of inflammation was treated with St. John's Wort, whether it was inflammation due to a skin condition or whether there was any evidence that hyperforin was actually responsible for the anti-inflammatory response. After all, according to HHP, St. John's Wort contains at least 9 other ingredients. The PTO's primary reference is silent on these points.

In fact, the PTO has asserted that "...at the time of the claimed invention, it would have been obvious to one of ordinary skill in art to optimize effective volumes and concentration as a matter of routine experimentation" and that one "would have been motivated to use hyperforin in a method of treating external anti-inflammatory conditions with a reasonable expectation of success because of its known benefit as disclosed by HHP." (Final Rejection at 4, first paragraph, at 6-7, bridging paragraph) However, a showing of motivation requires more than a blanket assertion of motivation without anything more. The Federal Circuit has emphasized this need in *In re San-su Lee*, 277 F. 3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002). The court stated that "...the factual showing for motivation is material to patentability, and could not be resolved on subjective belief and unknown authority." *Id.*

Additionally, the PTO's reliance upon Merck and the other secondary references does not cure the limitations in the HHP reference. These secondary references disclose various types of inflammatory skin disorders, *e.g.*, eczema, lichen simplex, chronic dermatitis. The PTO asks us to assume that a treatment of inflammation of one type would be a treatment for an inflammation of another type. This simply isn't true. Even if the HHP reference disclosed the use of hyperforin in a pharmaceutical to treat inflammation from a

skin disorder, (which it does not), there is no scientific reason to believe such treatment would be suitable for the specific disorders listed in claim 36 and in the rejected dependent claims. The PTO has failed to support the assumption that all substances that have anti-inflammatory properties are effective and safe for treating specific diseases that produce an anti-inflammatory response. Thus, one of skill in the art would not have an expectation of success based upon the PTO's selected combination of teachings.

Finally, Appellants argue that none of the cited references teach or suggest the use of hyperforin or hyperforin and hypericum for treating lymphoma or leukemia (claim 38), nor has the PTO made such an argument. The PTO's rejection is silent with regard to these embodiments. As such, the rejection lacks support with regard to this embodiment. As noted above, Appellants attempted to put these embodiments into an independent claim and to also have a separate claim directed to leukemia and lymphoma. However, the PTO refused to enter such amendments.

B. Claims 36, 38-45 and 56 would not have been rendered obvious over Valavichyus within the meaning of 35 U.S.C. § 103(a).

1. The Rejected claims

Claims 36, 38-45 and 56 have been discussed above.

2. The PTO's Case

The PTO asserts that Valavichyus teaches that extracts of St. John's Wort, specifically oil extracts, inhibit growth of sarcoma cells and tumor growth in animals. The PTO further asserts that it was well known in the art that oil preparations of St. John's Wort are hypericin-free and contain high concentrations of hyperforin, citing Chavez, *Monographs on Alternative Therapies in Hospital Pharmacy* 32: (12): 1621-1632 (1997) and that plant oils were used as pharmaceutical carriers (Final Rejection at 7-8).

The PTO concludes that although Valavichyus does not teach the method, volume, concentrations, mode of administration or purity of hyperforin, one of ordinary skill in the art could determine these amounts by routine experimentation. According to the PTO, one of ordinary skill in the art would have been motivated by routine practice to optimize the effective amounts of Valavichyus with a reasonable expectation for successfully treating cancer.

3. Appellants' Response

The PTO's obviousness rejection over Valavichyus is defective as a matter of fact and law. Here the PTO's error in fact relates to its interpretation of the cited art and its failure to acknowledge that claim 36 has been amended to remove "cancer". In any event, the cited references do not disclose what the PTO claims they do. Accordingly, one could not arrive at the invention from reading Valavichyus alone or in combination with Chavez and the rejection is therefore insupportable as a matter of law.

Specifically, the entire Valavichyus abstract states:

> The effect of oil extracts of the St. John's wort-hypericum perforatum and Chamomilla recutita on the growth of sarcoma 45 and Cholangioma PC-1 was studied in rats. The administration of the extracts inhibited the growth of tumors and increased the body weight of the animals. Data were presented on the effect of various doses of the extracts on the inhibition rate of the tumors.

It is not clear from this disclosure whether an oil extract of St. John's Wort or a combination of such extract with an oil extract of Chamomilla recutita was tested on mice tumors. Further, it is not clear what was in the oil extract of St. John's Wort. Was it only hyperforin? Or was it a combination of ingredients? How was the oil extract prepared? Was it prepared using olive oil on flowers as described in Chavez or was it prepared some other

way? Appellants have shown through the references of record in this case that St. John's Wort is a complicated plant containing many different ingredients. Different extracts from different parts of the plant contain different components and these components change with time and storage. The PTO attempts to address this issue by relying upon the teachings of Chavez.

Specifically at page 1622, Chavez teaches that "typically" oil preparations of St. John's Wort are prepared by extracting the flower with olive oil. It further states that such oil preparations are hypericin free and contain lipophilic compounds, including "sufficiently high" concentrations of hyperforin. What Chavez does not teach, however, is what else is the oil extract. What are the other lipophilic compounds? Also, it is not clear what is meant by "sufficiently high concentrations" of hyperforin. It is sufficiently high for what?"

It is clear that neither of the cited references teaches nor suggests, alone or in combination, a pharmaceutical composition comprising hyperforin that is 90% pure, as recited in claim 56. The PTO reads information into the cited references that is not actually there and then combines the alleged teachings to arrive at the invention. As such, the PTO's argument is based upon hindsight knowledge of the invention, which is an impermissible basis for an obviousness rejection.

As noted above, Appellants have amended claim 36 to remove "cancers." Thus, this rejection is arguably inapplicable with regard to claim 36. Also, claim 36 is directed to a method of treating by administering an effective amount of a composition **consisting of** hyperforin or **consisting of** hyperforin **and** hypercin and a pharmaceutically acceptable carrier. The cited references do not teach or suggest one or both of these active agents and the exclusion of other active agents. One could not arrive at the claimed invention by combining Valavichyus with Chavez. Nothing in either reference directs the skilled artisan to the use of hyperforin or hyperforin and hypercin in a pharmaceutical composition to treat any type of cancer, particularly those recited in the claims on appeal. Nothing in either

reference suggests what might be an effective amount of such compositions. Although Valavichyus might invite experimentation in the field of the invention, such an invitation cannot be a basis for an obviousness rejection.

The PTO's obviousness case is defective for yet another reason. Claims 36 and the other claims dependent thereon recite "a pharmaceutically acceptable carrier." This claim element is not taught or suggested by the cited references. And, in view of the specification, it is improper to construe Appellant's claims to equate St. John's Wort oil or extract with "a pharmaceutically acceptable carrier."

Even if one assumes that Valavichyus suggests oil extracts generally, such extracts, without more information are not pharmaceutically effective. The science presented in the specification shows that oil extracts of St. John's Wort is undesirable. The specification shows that actual skin cells (not a culture of cells many generations removed from the reality of disease processes in humans) were studied directly. That is, when Appellants treated real skin of living humans, and then studied cell samples scraped from those subjects, the plant oil (St. John's Wort oil) failed miserably and clearly was shown to be a bad carrier. (Specification at 19, last paragraph through the middle of page 20)

Appellants have obtained data from real *in vivo* studies that shows that Valavichyus's conclusions are wrong. A skilled artisan following Valavichyus would be led in the wrong direction. To the extent Valavichyus is relevant, it teaches away from the claimed invention. Such evidence of leading away is a further indication of unobviousness.

Appellants reiterate that the specification provides ample information regarding the desirable aspects of pharmaceutically effective carriers. As described in the specification (see Example 11 and associated text) St. John's Wort oil is not a pharmaceutically effective carrier. In the context of Appellants' specification, which teaches how to use the claimed invention, there is no reason to think that plant oils *per se* somehow are pharmaceutically

acceptable carriers. On the contrary, the oil studied (St. John's Wort) was not acceptable and it was found that the active ingredients can be combined with ethanol and cream, as described on page 6 first paragraph, ethanol and greasy ointment base (second paragraph of page 6). Ethanol is particularly useful for the pharmaceutically effective carrier (page 8, second paragraph) and "plant extracts" such as plant oils, if used, are used as ingredients, not carriers *per se*, as mentioned on page 8 lines 19-22. Crude plant oil extracts generally are not pharmaceutically acceptable. The specification at pages 8 and 9 describes carriers that are acceptable. Plant oil extracts are not in this list.

The PTO's assumption that "[i]t was also known in the art that plant oils were used as pharmaceutical carriers" (Final Rejection at 5) is simply not correct. A pharmaceutically acceptable carrier is not a plant oil extract. In fact, as discussed above, the specification provides data showing that a plant oil extract studied was not acceptable and that the plant oil has to be blended with acceptable materials (Specification at page 9, first three full paragraphs and Example 11).

Appellants further maintain that the above discussed data in the specification bolster the non-obviousness of their invention. Even if the PTO had presented a *prima facie* case of obviousness, the evidence presented in the specification would rebut such case. The specification teaches "pharmaceutically acceptable" carriers such as "ointment or cream" as, for example, stated on page 10, line 37. Particular advantages of this acceptable carrier are also stated on the bottom of page 37. The effects of the ointment and creams (representative pharmaceutically acceptable carriers) "is superior to that of the known St. John's Wort oil" as stated on page 11 lines 9 to 10 of the specification. This effect was previously generally unknown and unexpected. Another effect is that "penetration of active compounds" from these particular pharmaceutically acceptable carriers "is superior to that of active compounds from oils." Applicants note in this context that the word "oils" includes

plant oils such as plant oil extracts. Such plant oil preparations are NOT included within the group of pharmaceutically acceptable carriers, as is stated above.

Here, Appellants discovered to their surprise through investigation that the St. John's Wort ointment (*i.e.* with a pharmaceutically effective carrier) "brings about an inhibition of proliferation (of epidermal cells) . On the other hand, the use of St. John's Wort oil results in an increase in proliferation" as seen in the data of Figure 5 from the specification (see page 20 lines 14-18). Clearly, the claimed compositions (not with the plant oil as carrier but with an acceptable carrier) exhibited highly beneficial activity as unexpected results in comparison with the "natural" product promoted and taught by Valavichyus (and HHP). Although these unexpected results are strong evidence of unobviousness, in the Final Action at 9, first paragraph, the PTO states that Appellants failed to present "evidence" of unexpected results. Appellants counter that the PTO's failure to acknowledge and give weight to the evidence in the specification is improper and provides yet another basis to appeal this rejection.

C. Claims 36, 38-45 and 56 would not have been obvious over Valavichyus in view of HHP and/or DeCosterd within the meaning of 35 U.S.C. § 103(a).

1. The Rejected Claims

Claims 36, 38-45 and 56 have been discussed above.

2. The PTO's Case

The PTO rejects all the claims as being obvious over Valavichyus in view of HHP or DeCosterd, the secondary references being cited for allegedly teaching that extracts of St. John's Wort have anti-tumor properties. Specifically, the PTO states that "DeCosterd teaches extracts of Hypericum inhibit growth of colon carcinomas" and further teaches derivatives of hyperforin exhibit the growth-inhibiting activity (Final Rejection at 10). From this the PTO concludes that at the time of the invention, hyperforin, derivatives thereof and extracts of Hypericum were well known as effective agents against cancer of various kinds.

3. Appellants' Response

Appellants again point out that the claims on appeal do not recite "cancer." Thus, the applicability of this rejection is questionable. However, aside from this point, nothing in DeCosterd cures the deficiencies in the PTO's case, as set forth above in connection with the discussion of HHP and Valavichyus. DeCosterd teaches the isolation of two new compounds, hyperevolutin A and hyperevolutin B from the root bark of Hypericum revolutin VAHL. These compounds showed growth inhibitory activity against *in vitro* colon carcinoma cell line. Such a report does not direct the skilled artisan to Appellants' invention. Rather, it invites experimentation and further investigation. As such, it does not support an obviousness rejection.

VIII. CONCLUSION

It is respectfully requested that the Board pass the presently rejected claims on to allowance.

Respectfully submitted,

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By Patricia D. Granados
Patricia D. Granados
Registration No. 33,683

Customer No. 26633

Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W., Suite 300
Washington, DC 20006
(202) 912-2000 (telephone)
(202) 912-2020 (facsimile)

Appendix - Claims on Appeal

36. A method for treating a condition, comprising administering to a subject in need thereof an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, wherein said condition is selected from the group consisting of an inflammatory skin condition, a precancerous condition, a geriatric skin condition, and a microbial skin infection.

37. The method according to claim 36, wherein the condition is eczema.

38. The method according to claim 36, wherein said condition is selected from the group consisting of exsiccation eczemas, hyperkeratotic hand and foot eczemas, contact eczemas, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphomas, leukemia, an epithelial pre-cancerous condition, tumor metastases, and epithelial tumor.

39. The method according to claim 36, wherein said subject is a mammal.

40. The method according to claim 36, wherein said composition is in the form of a topical ointment and said effective amount consists of at least 15 μg hyperforin per ml of the composition.

41. The method according to claim 36, wherein said composition is in the form of a topical ointment and said effective amount is 0.02-20 mg hyperforin per ml of the composition.

42. The method according to claim 41 wherein said effective amount is 1-20 mg hyperforin per ml of the composition.

43. The method according to claim 42 wherein said effective amount is 10 mg hyperforin per ml of the composition.

44 The method according to claim 36, wherein said effective amount is at least 15 μg hypericin per ml of the composition.

45. The method according to claim 36, wherein said effective amount of hypericin is 20-150 μg hypericin per ml of the composition.

56. The method of claim 36, wherein said hyperforin is at least 90% pure.